Attorney Docket No. 1034008-000003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
David J. Burke et al.	Group Art Unit: 1644
Application No.: 10/773,406	Examiner: Yunsoo Kim
Filed: February 9, 2004	Confirmation No.: 6608
For: IMMUNOGLOBULIN FORMULATION AND METHOD OF PREPARATION THEREOF	

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, David Burke, hereby state as follows:

1. I am a citizen of the United States, residing at 5957 Chabolyn Terrace, Oakland, California, 94618, United States.

2. Attached are the details of my *curriculum vitae*.

3. My educational degrees include a Ph.D in Microbiology from SUNY Stony Brook, an M.S in Biochemistry from the University of Colorado, and a B.S in Chemistry from the University of Iowa (see details in attached CV).

4. From September 9, 1999, to the present, I have been employed by Elan Pharmaceuticals, Inc. ("Elan"), and currently hold the position of Senior Director of Biotechnology Development . Including my present position at Elan, I have over 25 years of experience in the pharmaceutical formulation development field, in particular in the area of protein formulation, including antibody formulations.

5. I am an inventor of the invention described and claimed in the present application, U.S. Patent Application No. 10/773,406.

6. I have reviewed in detail the Official Action mailed March 9, 2007, including the rejections raised therein and the documents cited by the Examiner. I

understand that claims 1-12, 15-17, 23, 29-32, 41, and 43-44 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 6,914,128 ("the '128 patent") in view of Gordon et al. (Gastroenterology, 2001, 121:268-274) ("Gordon")).

7. Independent claim 1 is directed to a stable, aqueous formulation comprising natalizumab, a phosphate buffer, a polysorbate, and sodium chloride.

8. The '128 patent discloses an antibody which is structurally different from natalizumab in significant ways. Natalizumab is a humanized monoclonal IgG4 antibody that targets the alpha4 subunit of alpha4beta1 and alpha4beta7 cell surface receptors. The antibody of the '128 patent is an IgG1 antibody which targets IL-12, a secreted protein. Since the antibody of the '128 patent and natalizumab have different antibody subclasses there are differences in the antibody constant regions. Further, since the antibodies have different targets, the variable regions are quite different. The structural differences between the antibody of the '128 patent and natalizumab are such that formulations that are effective with one antibody may not be effective with the other. In my experience, differences in either the constant regions or the variable regions of antibodies can lead to differences in optimum formulations, both with respect to choice of excipients and the concentration of both excipients and the antibody of interest. Thus, each antibody must be treated as a new chemical entity whose optimum formulation can only be arrived at by actual experiments.

9. As one of skill in the art, it is my opinion that the '128 patent is not a specific teaching because it discloses a large group of buffers and other formulation ingredients without appreciating any benefit that can result from a more specific selection of ingredients. Such a broad disclosure does not provide any real benefit to those of skill in the art. Despite this listing of potential ingredients, the '128 patent teaches the specific tailoring of the formulation to the specific antibody. Thus, while the '128 patent offers very little help to those skilled in the art to develop a formulation for any specific antibody, the '128 patent does recognize that the selection of ingredients in the formulation art is not one size fits all. Accordingly, I understand that the '128 patent teaches a formulation that must be tailored to the antibody.

10. Gordon discloses formulations containing natalizumab that were used in early clinical trials; however, the natalizumab formulations disclosed in Gordon are no longer used due to limited stability of the formulation. Thus, the formulations disclosed in Gordon are not suitable because they are not stable.

11. Thus, it is my opinion that the '128 patent combined with Gordon can not provide the stable natalizumab formulations recited in the present claims.

12. Antibody formulations differ in many unexpected ways including with regard to protein degradation, aggregation, deamidation, and oxidation.

13. I found that natalizumab was difficult to formulate into a stable and usable product for administration to patients. Although the ingredients of the formulation are individually known in the formulation art, the specific combination as presently claimed was found only after many attempts and years of research. Many different permutations and ingredients were tested before the stable formulation claimed in the present application was discovered and developed. The administration of a new drug and its formulation is a complex undertaking. Extensive research is required to arrive at a formulation which is ready and safe for dosing. Clinical trials of natalizumab began in 1995. Throughout clinical development, the dose of antibody required changed significantly, requiring several formulation changes to accommodate the changes in dose. In an iterative fashion, these dose changes were accompanied by changes in choice of excipients and in concentrations of excipients in order to maintain product quality and stability. In total, five different formulations of natalizumab were used during clinical trials. It was only after over ten years of effort that the claimed formulation was developed.

14. The present natalizumab formulation is a successful FDA approved drug product currently marketed by Elan Pharmaceuticals, Inc., under the tradename Tysabri® to treat relapsing forms of multiple sclerosis. Tysabri® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies. This formulation, administered intravenously to patients, has enjoyed a great deal of commercial success. As of the end of September 2007, in the United States approximately 10,500 patients were receiving Tysabri® with over 2,100 physicians prescribing the therapy, and

approximately 5,500 patients were receiving Tysabri® therapy in the European Union. Tysabri® is currently approved for marketing in more than 20 countries.

15. Accordingly it is my opinion that one of skill in the art would not be able to prepare a stable formulation containing natalizumab as presently claimed, simply by reading the disclosures of the '128 patent and Gordon.

16. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and/or imprisonment under Section 1001 of Title 18 of the United States Code.

DATE: 20 Nov 07 SIGNED: David Burke

David Burke

CURRICULUM VITAE

Name David James Burke

Work Address
Senior Director, Biotechnology Development
Elan Pharmaceuticals, Inc.
800 Gateway Blvd.
South San Francisco, CA 94080
Phone: (650) 616-2629
Email: david.burke@elan.com

Home Address
5957 Chabolyn Terrace
Oakland, CA 94618
(510) 652-6466

Industry Experience

1999-2005 Director, then Senior Director, Biotechnology Development
Elan Pharmaceuticals, Inc.

1997-1999 Senior Director, Analytical R&D,
Matrix Corporation

1995-1997 Director, Pharmaceutical Development
Xoma Corporation.

1987-1995 Director, Analytical Biochemistry,
Xoma Corporation.

1985-1987 Analytical Biochemist,
Xoma Corporation.

1981-1985 Group Leader, Senior Research Chemist
Bio-Rad Laboratories.

Academic Experience

1980-1981 Post Doctoral Fellow
Lawrence Berkeley Laboratory, Berkeley, CA

1977-1979 Post Doctoral Fellow
Dept. of Biochemistry, University of California, Berkeley, CA.

Education

Institution	Degree	Year	Department
SUNY, Stony Brook	Ph.D.	1977	Microbiology
University of Colorado	M.S.	1974	Biochemistry
University of Iowa	B.S.	1968	Chemistry

Areas of Expertise

- Analytical development, validation and characterization
- Formulation development and product stability
- Process development, validation and scale-up
- Regulatory filings for CMC sections

Current Responsibilities at Elan

- Elan CMC lead for development of Tysabri from Phase 2 through commercial launch and post launch activities. Member of joint (with Biogen Idec) manufacturing steering committee, joint project team, and CMC team.
- Elan CMC lead and joint project team member for AAB-001 (monoclonal antibody), ACC-001 (immunotherapy), and AAB-002 (monoclonal antibody) projects with Wyeth as partner.
- Responsible for timely preparation and review of CMC sections for BLA (CTD) and IND filings. Oversight of external scale-up activities, validation of production processes, analytical development/validation, and biochemical characterization activities.
- Head of Formulation Development group.

Prior Responsibilities at Matrix Pharmaceuticals

- Analytical development and validation for small molecule oncolytics
- Formulation development and stability for novel local delivery systems
- Project management activities for a novel nucleoside analog (FMDC)

Responsibilities at XOMA

- Analytical development, validation and biochemical characterization (antibodies, conjugates, recombinant proteins, peptides)
- Formulation development and stability studies

Responsibilities at Bio-Rad

- Development of a new line of HPLC ion-exchange resins designed for rapid separation and analysis of proteins, peptides, and oligonucleotides
- Development of column packing procedures for commercial use
- Development of a series of column applications (e.g. HbA1c quantitation) and promotional literature
- Development of lyophilized protein ion-exchange standards

Publications

1. D. Burke, P. Kaufman, M. McNeil, and P. Albersheim. 1974. The structure of plant cell walls. VI. A survey of the walls of suspension-cultured monocots. Plant Physiol. 54: 109-115.

2. K. Keegstra, B. Sefton, and D. Burke. 1975. Sindbis virus glycoproteins: effect of the host cell on the oligosaccharides. J. Virol. 16: 613-620.

3. D. J. Burke and K. Keegstra. 1976. Purification and composition of the proteins from Sindbis virus grown in chick and BHK cells. J. Virol. 20: 676-686.

4. D. J. Burke. 1977. Studies on the Sindbis Virus Glycoproteins. Ph. D. thesis. Department of Microbiology, SUNY at Stony Brook.

5. K. Keegstra and D. J. Burke. 1977. Comparison of the carbohydrate of the Sindbis virus glycoproteins with the carbohydrate of host cell glycoproteins. J. Supramol. Struct. 7:371-379.

6. D. J. Burke and K. Keegstra. 1979. Carbohydrate structure of Sindbis virus glycoprotein E2 from Virus grown in hamster and chicken cells. J. Virol. 29:546-554.

7. D. Burke, L. Mendonca-Previato, and C. E. Ballou. 1980. Cell-cell recognition in yeast: Purification of Hansenula wingei 21-cell sexual agglutination factor and comparison of the factors from three genera. Proc. Nat. Acad. Sci. USA 77:318-322.

8. L. Mendonca-Previato, D. Burke, and C. E. Ballou. 1982. Sexual agglutination factors from the yeast Pichia amethionina. J. Cell. Biochem. 19: 171-178.

9. R. M. Krauss and D. J. Burke. 1982. Identification of multiple subclasses of human low density lipoproteins. J. Lipid. Res. 23:97-104.

10. D. J. Burke, A. Kesaniemi, W. Beltz, S. M. Grundy, and R. M. Krauss. 1983. Metabolic properties of human low-density lipoprotein subclasses. Arteriosclerosis, 2:417.

11. D. J. Burke, J. K. Duncan, L. C. Dunn, L. Cummings, C. J. Siebert, and G. S. Ott. 1986. Rapid protein profiling with a novel anion exchange material. J. Chromat., 353:425-437.

12. D. J. Burke and J. K. Duncan. 1985. Very rapid microanalysis of IgG in ascites fluids by HPLC using a novel anion exchange column. In Proc. of the Symp. of Amer. Prot. Chem., Sept. 30-Oct. 3, 1985.

13. D. J. Burke, J. K. Duncan, C. J. Siebert, and G. S. Ott. 1986. Rapid microanalysis of hemoglobins and other proteins using a novel cation exchanger. J. Chromat. 359: 533-540.

14. R. Little, D. Kelner, E. Lim, D. Burke, and P. Conlon. 1994. Functional Domains of Recombinant Bactericidal/Permeability Increasing Protein (rBPI23). J. Biol. Chem. 266:1865-1872.

15. F. Castillo, L. Mullin, B. Grant, J. DeLeon, J. Thrift, L. Chang, J. Irving and D. Burke. 1994. Hybridoma Stability. In Genetic Stability and Recombinant Product Consistency, F. Brown and A. Lubinieki, eds. (Karger, 1994) vol. 83, pp. 55-64.

16. D.J. Burke and W.C. McGregor. 1994. Formulation and Stability of Murine IgM and of Ricin A Chain Immunoconjugates. Keynote address at the ACS National Meeting, San Diego, CA.

17. D. J. Burke. 1998. Affinity Chromatography and Related Techniques. In *Basic HPLC and CE of Biomolecules* by R. L. Cunico, K. M. Gooding, and T. Wehr (published by Bay Bioanalytical Laboratories).

18. Kuan Son I, Chang P, Lin JM, Burke D, Yu NY, Jones RE. 2000. Cytidine deaminase and the antiproliferative activity of FMdC. Proc Am Assoc Cancer Res 41: 490.

19. P. Chang, S. Kuan, G. Eberlein, D. Burke, and R. Jones. 2000. Characterization of bovine collagens using capillary electrophoresis – an alternative to slab gel electrophoresis. *J. Pharm. Biomed. Anal.* 22: 957-966.

Patents

1. G. Theofan, A. Horwitz, D. Burke, M. Baltaian, and L. Grinna. 1995. Stable Bactericidal/ Permeability-Increasing Protein Muteins. US patent 5,420,019.

2. Horwitz, S.F. Carroll, and D.J. Burke. 2000. Bactericidal/permeability-increasing protein (BPI) deletion analogs. US patent 6,087,126.

3. G. Theofan, A. Horwitz, D. Burke, M. Baltaian, and L. Grinna. 2002 and 2004. Stable Bactericidal/permeability-increasing protein products and pharmaceutical compositions containing the same. US patents 6,433,140 and 6,828,418.

4. D.J. Burke and S.I. Kuan. 2004. Oxidized collagen formulations for use with non-compatible pharmaceutical agents. US patent 6,673,370.

5. D.J. Burke, S. Buckley, R. Lehrman, B. O'Connor, and J. Callaway. Immunoglobulin formulation and method of preparation. Patent applied for, 2004.